The specification has also been amended to include a Sequence Listing in compliance with 37 CFR 1.821-1.825. A computer readable form of the new Sequence Listing is contained on the 3.5 inch diskette enclosed with this response along with the appropriate Declaration.

For clarity, as described more fully below, claim 24 was amended to describe the term "closely packed" more particularly, and the phrase "each of" was deleted.

No new matter has been added by the amendments. Reconsideration is respectfully requested.

**The Invention**

The present invention is directed to clonal populations of polynucleotides that are arranged in a planar array in useful quantities for analysis by means of microparticles. Each different polynucleotide is attached to a different microparticle, or microbead, in duplicate copies (i.e. a clonal population), and such polynucleotide-containing microparticles are disposed in a closely packed planar array. This permits the analysis of large numbers of polynucleotides at the same time by a single analytical instrument.

To assist the Examiner's understanding of the invention, Applicants have enclosed a copy of a recent publication (Brenner et al, Nature Biotechnology, 18: 630-634 (2000)(Exhibit B)) in which the present invention was featured on the cover of the issue.

**Rejections under 35 U.S.C. 112 Second Paragraph**

The Examiner rejected claims 24-28 under 35 USC 112 second paragraph as being confusing because of the phrase "closely packed planar array of microparticles," and the description of microparticle packing in claim 25.

Applicants respectfully disagree with the Examiner, especially in view of the amendments. Claim 24 has been amended to include the description of closely packed microparticles from claim 25, and claim 25 has been cancelled, thereby also obviating the Examiner's concern over the use of the phrase "in reference."

In regard to the Examiner's request that the description of microparticle packing be clarified, Applicants direct the Examiner's attention to page 6, lines 18-24, and to Fig. 3a of the specification. There, the phrase "at least eighty percent of the number of microparticles in a hexagonal array of equal area" is explained. In particular, the term "hexagonal array" is explained and illustrated in Fig. 3a. Applicants submit that with such explanation and illustrations in the specification the meaning of phrase would be clear to one of ordinary skill in the art. Applicants further submit that the alternative description of microparticle packing is

clear on its face. That is, the average distance of microparticles next to one another in an array must be less than two microparticle diameters.

In view of the above, Applicants respectfully request that the rejection under 35 USC 112 second paragraph be withdrawn.

**Rejections under 35 U.S.C. 103(a)**

The Examiner rejected claims 24-27 under 35 USC 103(a) as being unpatentable over Dower (U.S. patent 5,708,153). The Examiner argues that Dower discloses the combinatorial synthesis of oligonucleotides on microparticles using a plurality of reaction vessels, but does not disclose the disposition of microparticles in a planar array or the attachment of cDNAs to microparticles. Nonetheless, the Examiner reasons that because peptide synthesis in arrays is known (as mentioned in the "Background of the Invention" section of Dower), it would be obvious to one of ordinary skill in the art to produce Applicants' polynucleotide arrays.

Applicants respectfully disagree with the Examiner for the following reasons. First, as the Examiner points out, Dower neither discloses nor suggests planar arrays of microparticles having polynucleotides or oligonucleotides attached, which is an important element of Applicants' invention (e.g., the planar configuration in Applicants' invention permits the simultaneous detection and monitoring of many tens of thousands of optical signals from the polynucleotides attached to different microbeads). In particular, Dower neither discloses nor suggests any reason why one of ordinary skill would be interested in forming a planar array of microparticles with polynucleotides attached, particularly in the closely packed configuration called for in Applicants' invention. This is because the sole thrust and objective of the invention in Dower is the combinatorial synthesis, selection, and identification of individual compounds from a large diverse family (see Figures and Summary of Invention) for the purpose of identifying drugs (col. 17, lines 14-21). In contrast, Applicants' invention is a component of a system for simultaneously analyzing very large numbers of different analytes using an optical detection means (see claim 1, page 31, lines 4-13, of the specification).

Second, to the extent that Dower teaches identification of compounds on microparticles, the preferred method is fluorescence activated cell sorting (FACS), or like technique (col. 17, lines 29-34). In this technique, microparticles in a fluid (not a planar array) are analyzed in a serial manner as they pass single-file by a detection station in a fluid stream or jet (in contrast to Applicants' invention where massive numbers of microparticles immobilized in an planar are simultaneously imaged for detection, Fig. 1a, and page 2, line 35, to page 3, line 2). Thus, Dower in fact teaches away from this feature of Applicants' invention.

Third, Applicants take exception to the Examiner's suggestion that the term "oligonucleotide" in Dower would be understood to include a cDNA or that a plurality of

oligonucleotides would be understood to include a cDNA library by one of ordinary skill in the art. The primary use of oligonucleotides in Dower is for identifying the composition of a compound co-synthesized on the same microparticle (col. 2, line 65, to col. 3, line 18, and Fig. 2). Moreover, the term "oligonucleotide" is defined in Dower (col. 5, lines 20-32) to be in the range of 50-150 nucleotides, which clearly does not contemplate the full range of cDNAs in a typical library. cDNA libraries contain individual species from several hundred basepairs to several thousand basepairs in length (Current Protocols in Molecular Biology, Ausubel et al, Editors, report in Unit 5.6 that in a cDNA library "most of the cDNA should be >1.5 kb." Also see Fig. 5.6.1 of the same reference which illustrates the size separation of a typical cDNA library by gel electrophoresis. Co-separated size markers indicate a size range of from several hundred basepairs to 20 kb. Copies of this excerpt are attached as Exhibit D). The important point is that Dower nowhere discloses or suggests how to attach identical copies of cDNAs from a plurality to the same microparticle. Dower discloses synthetic oligonucleotides with this property, but not cDNAs.

Finally, Applicants respectfully disagree that a suggestion in Dower that the disclosed synthetic approach could be carried out on pins adapted for use with a conventional 96-well array would in any way lead one of ordinary skill in the art to Applicants' invention, absent independent inventive acts. Applicants direct the Examiner's attention to Exhibit C which contains a full sized photocopy of both a conventional 96-well array and a flow cell of Applicants' invention containing an array of microparticles with polynucleotides. The microparticles of Applicants' invention (which cannot be individually resolved in the photocopy) are disposed in the channel which can be identified as the darkened region along the longitudinal axis of the rectangular slide. Applicants submit that there is no way that pins or microparticles associated with the wells of 96-well plate could even be within the bounds of Applicants' invention as claimed. Furthermore, the scale (5 mm well diameter v. 1.7 mm width of entire array of disclosed embodiment--"210" in Fig. 2B and page 22, lines 17-18), shape (wells in retangular array format v. microparticles in random or hexagonal array format--Fig. 3A-D), and general configuration (e.g. 96-well plates are used for so-called "batch" processing v. microparticles in flow chamber are involved in a "flow-through" analytical process) of the two pieces of equipment are so strikingly different that one of ordinary skill in the art would not be led from one to the other without a significant inventive contribution.

Accordingly, Applicants respectfully request that the above rejection under 35 USC 103(a) be withdrawn.

The Examiner rejected claims 24 and 28 under 35 USC 103(a) as being unpatentable over Dower ('153) in view of Matson (U.S. patent 5,429,807). The Examiner apparently reasons

that Dower teaches planar arrays of microparticles having polynucleotides attached and Matson teaches flow chambers; therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Dower with those of Matson to arrive at Applicants' invention.

Applicants respectfully disagree with the Examiner's analysis. First, Applicants disagree that Dower either teaches or suggests planar arrays of microparticles having polynucleotides attached, for the reasons given above.

Second, Matson discloses an approach for manufacturing microarrays of oligonucleotides (similar to those sold by Affymetrix or Rosetta) using (in the preferred emodiments) an applicator consisting of a series of parallel channels (e.g. Fig. 6) for delivering fluid reactants to predetermined positions on a solid phase planar support (e.g. glass or polypropylene, col. 4, line 60, to col. 5, line 8) which is held in an applicator assembly (e.g. Fig. 6). Applicants submit that Matson neither discloses nor suggests any use whatsoever of microparticles and that Matson in fact teaches away from Applicants' invention because it is fundamentally incompatible with the use of microparticles as substrates. In order for Matson's process to work, the applicator must be repeatedly reoriented with respect to the planar support while the growing chains of oligonucleotides on the support remain in fixed positions. This of course could never happen in such a system with microparticles because they are completely mobile. Furthermore, there is nothing in either Dower or Matson that would lead one of ordinary skill in the art to combine the particulate supports of Dower (which are used to enable combinatorial "split and mix" synthesis) with the reagent applicator of Matson (which is used to enable non-combinatorial synthesis of defined oligonucleotides at defined positions on a planar support).

Accordingly, Applicants respectfully request that the above rejection under 35 USC 103(a) be withdrawn.

In view of the above, Applicants submit that the claims as written fully satisfy the requirements of Title 35 of the U.S. Code, and respectfully request that the rejections thereunder be withdrawn and the claims be allowed.

If any additional time extensions are required, such time extensions are hereby requested. If any additional fees not submitted with this response are required, please take such fees from deposit account **12-2491**.

Respectfully submitted,

Stephen C. Macevicz
Reg. No. 30,285
Attorney for Applicants

Telephone: (510) 670-9365

Enclosures:

Declaration of Sequence Listing with 3.5 inch diskette
Petition for Time Extension for Response
Copy of Brenner et al, Nature Biotechnology, 18: 630-634 (2000)
Copy of Excerpts from Current Protocols in Molecular Biology